BISBUBSTRATE INHIBITORS OF KINASES

Abstract of the Invention

Protein kinase inhibitors have applications as anti-cancer therapeutic agents and biological tools in cell signalling. Potent and selective bisubstrate inhibitors for the insulin receptor tyrosine kinase are based on a phosphoryl transfer mechanism involving a dissociative transition state. One such inhibitor is synthesized by linking ATPγS to a peptide substrate analog via a two-carbon spacer. The compound is a high-affinity competitive inhibitor against both nucleotide and peptide substrate and shows a slow off-rate. A crystal structure of this inhibitor bound to the tyrosine kinase domain of the insulin receptor confirms the key design features inspired by a dissociative transition state, and reveal that the linker takes part in the octahedral coordination of an active site Mg^{2+} ion.